expression of transgene. Transgene expression following exposure to the reporter gene was assessed by enzyme activity (Galacto-Light assay) and by a histochemical method after X-Gal staining. Transgene expression following transfection with eNOS was assessed by histochemical staining and enzyme activity was assessed by the conversion of L-arginine to L-citrulline. After gene transfer, ß-galactosidase or eNOS were expressed in endothelium and adventitia but not media. Enzyme activity of eNOS or the reporter gene transfer was greater in the pulmonary artery of patients with scleroderma than in control arteries. Effects of transgene expression on vascular function were examined by recording isometric tension 1 day after transduction. After precontraction with phenylephrine, acetylcholine produced significantly less relaxation in vessels from scleroderma than in vessels from normal arteries. Relaxation in response to acetylcholine was greater in pulmonary arteries from both normal and scleroderma arteries that were transfected with AdeNOS than in vessels treated with vehicle or Adbetagal. Vasorelaxation in response to acetylcholine was inhibited by N-omega-nitro-L-arginine. Responses to sodium nitroprusside were similar after treatment with vehicle alone, Adbetagal, or AdeNOS in both groups of arteries. Thus, overexpression of eNOS with an adenoviral vector improves impaired NO-mediated relaxation in human pulmonary arteries and that adenoviral gene-transfer expression is greater in the pulmonary arteries from patients with scleroderma than from normal human controls.

1081-78 Thrombin Generation After the Abrupt Cessation of Intravenous Unfractionated Heparin Is Mediated by the Extrinsic Coagulation Pathway

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A "rebound" increase in prothrombotic potential has been observed biochemically and clinically after the abrupt cessation of unfractionated heparin (UFH) among patients with acute coronary syndromes. The responsible mechanism(s) have not been determined. **Methods:** In a single-center pilot study, 30 patients with either unstable angina or non-ST segment elevation MI who had received a continuous IV infusion of UFH for 48h underwent serial blood sampling for markers of thrombin generation (F1.2), intrinsic pathway activation (factor XIIa) and extrinsic pathway activation (factor VIIa, tissue factor pathway inhibitor [TFPI]) immediately before (baseline) and 1h, 4h, and 24h after treatment was terminated. The **Results** are summarized below. **Conclusions:** Thrombin generation increases progressively after UFH cessation and correlates with activation of the extrinsic but not the intrinsic coagulation pathway. Future investigation should focus on the effects of pharmacologic thrombin antagonist-mediated prothrombotic potential and the specific contribution of impaired tissue factor-directed vascular thromboresistance.

Coagulation Measurements Over Time (mean values)

Time Point	Heparin	F1.2	Factor XIIa	Factor VIIa	TFPI
	(U/ml)	(nM)	(ng/ml)	(mU/ml)	(ng/ml)
Baseline	0.56	2.22	3.08	38.7	126.6
1h	0.34	2.36	3.17	32.2	87.7
4h	0.12	2.84	3.63	62.6*+	72.2*++
24h	0.00*	4.40*	2.75	48.4+	85.3*++

*Compared to baseline value, p=0.001; +correlation with F1.2 (r=0.85)++; inverse correlation with F1.2 (r=0.82 and 0.78, respectively)

1081-79 Long-Term Treatment With Phosphodiesterase Type 5 Inhibitor Improves Pulmonary Hypertension Caused by Congestive Heart Failure Through a Natriuretic Peptides-cGMP Pathway

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BACKGROUND: Congestive heart failure (CHF) accompanies pulmonary hypertension (PH) and PH is an independent predictor of mortality in patients with CHF. Natriuretic peptides (NPs) system is activated in CHF and regulates pulmonary vascular tone, however, the degradation of cGMP in pulmonary vasculatures is accelerated by phosphodiesterase type 5 (PDE5) in CHF. METHOD: To examine (1) whether long-term treatment with a specific PDE5 inhibitor ameriolates PH, we administered T-1032 (1 mg/kg/day, n=7) to dogs with CHF induced by rapid pacing (270 beats/min, 22 days), and CHF control dogs were given placebo (n=7); and (2) whether NPs-cGMP pathway is involved in the therapeutic effects of T-1032 on PH, we injected a specific NPs receptor antagonist, HS-142-1 (HS, 3 mg/kg) to dogs after long-term treatment with T-1032. RESULTS: In this experimentally produced CHF, mean pulmonary pressure (MPAP) and the ratio of right ventricular weight/body weight (RV/BW) were significantly increased from 16 to 31 mmHg, from 1.4 to 2.3, P<0.001, respectively. Plasma atrial natriuretic peptide (ANP) and cGMP levels were also higher than the normal dogs (460 vs 46 pg/ml, P<0.001 and 35 vs 15 pmol/ml, P<0.01, respectively). Long-term treatment of T-1032 further increased plasma cGMP level compared with the CHF control dogs (72 vs 35 pmol/ml, p<0.05) despite no significant difference in plasma ANP levels (424 vs 460 pg/ml). Without adverse hypotensive effect on systemic blood pressure (BP, 94 vs 87 mmHg), T1032 significantly decreased MPAP and RV/BW by 26 % and 18 %, respectively (P<0.05) compared with those of the CHF control dogs. In the T-1032 group, HS significantly suppressed plasma cGMP level from 72 to 40 pmol/ml, p<0.05. MPAP but not BP was elevated from 23 to 29 mmHg, p<0.05. In the CHF control group, HS also decreased plasma cGMP level from 34 to 10 pmol/ml (p<0.05) but did not affect MPAP. CONCLUSION: Long-term treatment with T-1032 exerts an important role in the regulation of PH through the NPs-cGMP pathway without hypotensive effect in CHF. PDE5 inhibitor may be an attractive therapeutic agent for CHF-induced PH.

1081-80 Effects of the Oral Endothelin Receptor Antagonist Bosentan on Echocardiographic and Doppler Measures in Patients With Pulmonary Arterial Hypertension

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Background: Bosentan, an orally active dual endothelin receptor antagonist, improves symptoms, exercise capacity, and hemodynamics in patients with pulmonary arterial hypertension. In the present study, the effects of bosentan (125 or 250 mg bid) on echocardiographic and Doppler variables were analysed in a subgroup of 85 patients with WHO class III and IV pulmonary arterial hypertension enrolled in the prospective, double blind, placebo-controlled BREATHE-1 study.
Methods: The majority of patients (84%) had primary pulmonary hypertension. 29 patients received placebo and 56 received bosentan in a 1:2 randomization procedure. 6-minute walk tests and echocardiograms were performed at baseline and after 16 weeks. Echocardiograms were recorded in 13 centers and measurements were performed in a core laboratory.
Results: Baseline clinical, hemodynamic and echocardiographic characteristics were similar in the placebo and bosentan groups. On baseline evaluation, echocardiographic and Doppler variables were consistent with marked abnormalities of right (RV) and left (LV) ventricular structure and function. The treatment effect (difference between treatment groups in the mean change at week 16) on 6-minute walking distance was 37 m in favor of bosentan (p = 0.036). Time velocity integrals of the LV outflow tract and of mitral inflow were improved in the bosentan group and resulted in a treatment effect on Doppler-derived cardiac index of + 0.4 l/min/m^2 (p = 0.007). Treatment effects of bosentan on other echocardiographic and Doppler parameters were as follows: E/A ratio = + 0.18 (p = 0.004), LV end-diastolic area = + 4.2 cm^2 (p = 0.003), LV systolic eccentricity index = - 0.12 (p = 0.047), RV end-systolic area = - 2.3 cm^2 (p = 0.057), LV/RV diastolic areas ratio = + 0.16 (p= 0.04), RV diastolic remodeling index (minor/major axis ratio) = - 0.06 (p = 0.004), RV ejection time = + 22 msec (p = 0.007), Doppler RV (Tei) index = - 0.06 (p = 0.03), inferior vena cava minimum diameter = - 0.22 cm (p = 0.03), pericardial effusion score = - 0.54 (p = 0.05).
Conclusions: Bosentan improves RV systolic function and LV early diastolic filling and leads to reverse ventricular remodeling in patients with pulmonary arterial hypertension.

1081-81 Oral Sildenafil Is an Effective and Specific Pulmonary Vasodilator in Patients With Pulmonary Arterial Hypertension

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Background: The prognosis of patients with severe pulmonary hypertension (PHT) is poor. To determine prognosis and guide chronic therapy, an acute trial of a selective pulmonary vasodilator, usually inhaled nitric oxide (iNO), is performed during cardiac catheterization. We hypothesized that oral sildenafil, a phosphodiesterase V inhibitor, is a safe and effective alternative to iNO.
Methods: We studied 12 consecutive patients (mean±SEM, 43±2 years, 8 female) referred during one year, for consideration of heart-lung transplantation or as a guide to medical therapy. All but one were functional class IV. Subjects had primary PHT (8), pulmonary arterial hypertension (2) or secondary PHT (2). Hemodynamics and serum cyclic guanosine monophosphate levels (c-GMP) were measured at baseline and at peak effects of iNO (80 ppm), sildenafil (75 mg) or their combination.
Results: The decrease in pulmonary vascular resistance was similar with iNO (-20±6%) and sildenafil (-25±3%) while sildenafil+iNO was more effective than iNO alone (-32±5%, p<0.03). Sildenafil and sildenafil+iNO increased cardiac output (15±6 and 15±4%, respectively) whereas iNO did not (0.3±3.0%, p<0.003). iNO increased, whereas sildenafil tended to decrease pulmonary-capillary wedge pressure (+17±7 versus -9±8%, p< 0.001). Systemic arterial pressure was similar amongst groups and did not decrease with treatment. cGMP levels increased similarly with iNO and sildenafil and their combination elevated cGMP more (p<0.05).
Conclusions: A single oral dose of sildenafil is as effective and selective a pulmonary vasodilator as iNO. Sildenafil may be superior to iNO in that it causes greater increase in cardiac output and does not increase wedge pressure. Future studies are indicated to establish whether sildenafil could also be effective chronically.

POSTER SESSION

1082 Pharmacology/Hormones: Basic I

Monday, March 18, 2002, 9:00 a.m.-11:00 a.m.
Georgia World Congress Center, Hall G
Presentation Hour: 9:00 a.m.-10:00 a.m.

1082-72 Carbon Monoxide Decreases Pulmonary Vascular Resistance and Blocks Hypoxic Pulmonary Vasoconstriction in the Rat

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The effects of carbon monoxide (CO) and the heme oxygenase inhibitor chromium mesoporphyrin (CM) on the pulmonary circulation was investigated in the intact-chest rat. Pulmonary arterial (PA) and wedge pressures were measured using a newly developed right-heart